

**COMBINATIONS OF VASOPROTECTIVE AGENTS AND  
FORMULATIONS CONTAINING THEM**

**FIELD OF THE INVENTION**

The present invention relates to combinations of vasoprotective agents useful for the prevention and the treatment of vascular injuries induced by an excess of plasma lipids.

5       The combinations of the invention reduce blood cholesterol and triglyceride levels while protecting the vascular wall against the injuries induced by overproduction of free radicals and cholesterol oxidized forms, thus strengthening the wall.

**DISCLOSURE OF THE INVENTION**

10       The present invention relates to combinations of vasoprotective agents and compositions comprising said combinations.

The arteriosclerotic disease is a very complex phenomenon not only connected with lipid conditions, therefore any synergetic actions concerning vascular protection and reduction of free radicals overproduction have large  
15       therapeutic interest. Chronic degenerative diseases such as cardiovascular diseases do not have a single origin. High triglyceride and cholesterol levels, accompanied by altered ratios of the lipoprotein fractions, as well as hypertension, undoubtedly induce marked vascular injuries with unfavourable prognosis. There is therefore the need to decrease blood cholesterol and  
20       triglycerides levels, while strengthening and protecting the arterial walls.

It has now been found that this objective can advantageously be attained by combining vasoprotective agents having different mechanisms of action.

The invention relates in particular to pharmaceutical, dietetic or nutritional compositions comprising:

25       - one or more polycosanols or esters thereof, either pure or as extracts;

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- ocotrienol and/or lycopene, preferably tocotrienol;
- one or more procyanidole oligomers optionally complexed with phospholipids;
- a vegetable oil rich in  $\omega$ -3,  $\omega$ -6 unsaturated fatty acids.

5       The hypocholesterolemizing, or more generally anti-atherosclerotic, activity of each single component of the combination is known, but only through the combined use thereof particularly remarkable preventive or therapeutic effects can be attained.

10       The use and the preparation of procyanidole oligomers complexed with phospholipids as anti-atherosclerotic agents are disclosed in WO 99/29331.

      Polycosanols, as well as  $\omega$ -3,  $\omega$ -6 unsaturated fatty acids, have been the object of investigations in the cardiologic and cardio-vascular fields for some time (*Int J Clin Pharm Res* 1994;14:27-33 and *Ann. Intern. Med.* 1999;130:554-62, respectively) while tocotrienol and lycopene, belonging to  
15       the family of carotenoids, have been extensively studied as agents able to prevent lipoperoxidation and formation of free radicals, and also as chemo-preventive agents (*Clin. Biochem* 1999;32:309-19).

      The polycosanols used according to the invention are straight, long chain aliphatic alcohols, typically straight alcohols having 24 to 30 carbon  
20       atoms, obtainable by saponification of waxes from vegetable materials such as olive, wheat, rice, sugar cane and other sources. These compounds can be used either in the free form or esterified with ferulic acid or other cinnamates variously substituted at the phenyl moiety, such as p-NO<sub>2</sub>, p-OH, and m-Cl cinnamates.

25       The procyanidole oligomers for use according to the invention can be obtained from *Vitis vinifera*, *Camellia sinensis*, *Aesculus hippocastanum*, *Olea europea*.

      The vegetable oil is preferably selected from *Enothera biennis*, *Ribes*

*nigrum* or *Portulaca oleracea* oils, more preferably *Enothera biennis* oil. The  $\omega$ -3,  $\omega$ -6 unsaturated fatty acids present in said oils can optionally be transformed into the corresponding alkyl esters, in particular the corresponding ethyl esters, by transesterification, for example by treating the oil with ethanol and H<sub>2</sub>SO<sub>4</sub> in the presence of benzene to azeotropically remove water.

The compositions of the invention can further contain luteolin per se or in the form of 7,3',4'-hydroxyethyl derivatives.

The formulations of the invention can contain 5 to 30 mg, preferably 15 mg, of polycosanols; 1 to 50 mg, preferably 8 mg, of tocotrienol or lycopene; 30 to 200 mg of proanthocyanidins or 100 to 320 mg of proanthocyanidins complexed with phospholipids, and 150 to 300 mg of vegetable oils, per unit dosage form.

20 Patients suffering from essential hyperlipidemia with carotid plaques were treated with a formulation of the invention having the following composition:

Rice polycosanols (70% polycosanols)	15 mg
Tocotrienol	14 mg
Procyanidole oligomers/phospholipids	320 mg
<i>Enothera biennis</i> oil	q.s. to 500 mg

20 After two month treatment with two capsules/day, patients showed normalized lipid parametres and improved conditions of the plaques, as evidenced by EcoDoppler.

The following examples illustrate the invention in greater detail:

#### Example I

25	Polycosanols from rice or olive residues oils	15 mg
	Tocotrienol	14 mg
	Procyanidole oligomers/phospholipids	320 mg
	<i>Enothera biennis</i> oil	q.s. to 500 mg

**Example II**

	Polycosanols from olive residues oil esterified with ferulic acid	30 mg
	Tocotrienol	14 mg
5	Procyanidole oligomers/phospholipids	250 mg
	<i>Enothera biennis</i> oil	q.s. to 500 mg

**Example III**

	Octacosanyl ferulate	12 mg
	Tocotrienol	12 mg
10	Epigallocatechin gallate/ phosphatidyl choline 1:1	250 mg
	Ethyl eicosapentanoate	q.s. to 500 mg

**Example IV**

15	Polycosanols from rice or olive residues oils esterified with ferulic acid	15 mg
	Tocotrienol	14 mg
	Procyanidole oligomers/phospholipids	250 mg
	<i>Enothera biennis</i> oil	q.s. to 500 mg

**Example V**

20	Polycosanols from rice or olive residues oils	15 mg
	Tocotrienol	14 mg
	Procyanidole oligomers	150 mg
	<i>Enothera biennis</i> oil	q.s. to 500 mg